Supplementary materials: Orienting the causal relationship between imprecisely measured traits using GWAS summary data

## S3 Text. The influence of unmeasured confounding on the inference of causal directions

We have assumed no unmeasured confounding in these simulations. Unmeasured confounding will however have potentially large influences on mediation-based methods for inferring causal directions, and can also adversely influence the estimate of the causal direction for the Steiger test.

### Unmeasured confounding in mediation

Including an unmeasured confounder, , after ignoring intercept terms the exposure and outcome variables can be modelled as

The observational estimate of the causal effect of on , is obtained from

From this it is clear that and will differ when both and are non-zero. Relating to mediation, where we attempt to test if associates with after adjusting for , such that

and

should any amount of unmeasured confounding exist, therefore, there will remain an association between and , which will introduce errors in inferring causal directions.

### Unmeasured confounding in the MR Steiger test

Similarly, we can investigate the extent to which unmeasured confounding will lead to the wrong causal direction between and using the MR Steiger test, evaluating the liability for the inequality being incorrect. After some algebra

and

S2 fig shows the relationship between the magnitude of the correlations between , and the confounder for a range of , and a range of confounder effects. The pattern of results were similar for different values of . We note that in most cases for the parameter values explored, where the observational absolute is less than 0.2, unmeasured confounding will not incur the wrong causal direction in the MR Steiger test.